An Oral Administration Form

The invention relates to an oral administration form containing at least one genus of probiotic microorganisms, said administration form itself and/or said probiotic microorganisms having at least one enteric coating.

Many people, particularly in economically and industrially highly developed nations, frequently complain of temporary or chronic indigestion caused by a damaged or impaired intestinal flora. These "diseases of the affluent society" mostly are caused by stress situations, abuse of medications or drugs, consecutive symptoms of treatments with antibiotics, but also by malnutrition in many cases. Acute and severe symptoms can be treated using well-known drugs which may contain not only suitable pharmaceutical active substances but also appropriate natural enzymes or intestine-specific microorganisms.

However, in case of chronic, mild disorders of the intestinal tract not actually to be referred to as a disease, habitual consumption of suitable, selected foods or dietary supplementing preparations based on probiotic microorganisms frequently is sufficient to alleviate or eliminate the symptoms caused by an impaired or damaged intestinal flora. Even in case of an intact or healthy intestinal flora, the supply of probiotic microorganisms, particularly in combination with antioxidants, may have an immunostimulating effect.

For these reasons, yoghurt and curdled milk products become more and more popular. However, most of these products which are valuable in nutrition and include suitable probiotic microorganisms for this purpose are fresh products and

can only be stored under refrigeration, and even in this event, for just a few days.

Furthermore, there are products presenting suitable probiotic microorganisms in the form of a monopreparation. However, these products involve the disadvantage of lacking approval as food or food supplement in many countries because they do not contain any further nutrition-physiologically valuable substances such as minerals, fats, vitamins, carbohydrates, proteins, roughage, or trace elements.

Moreover, an average of only about 10% of the ingested probiotic microorganisms are capable of developing their healthful activity in the human or animal intestine. Therefore, a substantially larger amount of probiotic microorganisms than required in therapeutic terms has to be ingested in order to achieve a sufficiently high activity of these probiotic microorganisms in the human and animal intestine and thus, a healthful effect.

It was therefore the object of the invention to increase the activity of probiotic microorganisms in the human and/or animal intestine and thus, their healthful effect as well.

According to the invention, said object is accomplished by providing an oral administration form containing at least one genus of probiotic microorganisms, said administration form itself and/or said probiotic microorganisms having at least one enteric coating.

The oral administration preferably is a tablet, a coated tablet, a capsule, a granulate, or a powder, more preferably a tablet, with multilayer tablets being particularly preferred.

All those microorganisms are suitable as probiotic microorganisms which themselves normally occur in a healthy human or animal intestine and/or have a healthful effect on a healthy, impaired or diseased intestinal tract. For example, probiotic microorganisms promote the intestinal digestion of lactose in individuals exhibiting a lactose incompatibility, or promote more rapid convalescence from various diarrhetic diseases. Preferably, the probiotic microorganisms employed are lactobacilli, bifidus bacteria, or streptococci, with *Lactobacillus casei*, *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, and/or *Lactobacillus plantarum* being particularly preferred.

The amount of probiotic microorganisms in the oral administration form of the invention is to be selected in a way so as to ensure the desired healthful effect. The oral administration form of the invention preferably contains from 10^3 to 10^{12}, more preferably from 10^5 to 10^{11} probiotic microorganisms, with 10^7 to 10^{10} being particularly preferred. For stability with respect to number and activity of living microorganisms, the materials used, particularly the carrier material having embedded the probiotic microorganisms therein, advantageously have a water content as low as possible. The water content preferably is ≤3.0 wt.-%, more preferably ≤0.1 wt.-%, relative to the weight of the carrier material.

According to the invention, the oral administration form has at least one enteric coating. In a preferred embodiment, the oral administration form of the invention has at least one coating essentially consisting of shellac or of shellac and polyvinylpyrrolidone.

In another preferred embodiment, the oral administration form of the invention has at least one coating comprised of at least two layers, one layer essentially consisting of hydroxypropylmethylcellulose, methylcellulose and/or polyvi-

nylpyrrolidone, and/or one layer essentially consisting of shellac or of shellac and polyvinylpyrrolidone.

In another preferred embodiment, the oral administration form of the invention has at least one coating comprised of at least two layers, the/one inner layer in the proximity of the core essentially consisting of hydroxypropylmethylcellulose, methylcellulose and/or polyvinylpyrrolidone, and/or the/one outer, off-core layer essentially consisting of shellac or of shellac and polyvinylpyrrolidone.

The oral administration form of the invention preferably includes from 1 to 10 wt.-% shellac, more preferably from 1.5 to 6 wt.-%, relative to the total weight of the oral administration form, with 2 - 3.5 wt.-% being particularly preferred.

Essentially, the oral administration form of the invention has an enteric coating of at least such a size so as to entirely enclose the probiotic microorganisms.

Another preferred embodiment of the oral administration form includes probiotic microorganisms which themselves are provided with an enteric coating. To this end, the probiotic microorganisms are dried using various methods well-known to those skilled in the art and subsequently provided with at least one enteric coating.

Also, in addition to the enteric coating(s), the inventive oral administration form itself and/or the probiotic microorganisms optionally may have one or more additional coating(s). Preferably, this/these coating(s) serves/serve to achieve improved adherence of the enteric coating(s) and/or improved flavor, stability and/or optical appearance.

The coatings can be coated both from an aqueous solution and from an organic solution. As for the oral administration form of the invention, it is advantageous to coat the first coating, i.e., the first or inner layer close to the core from an organic solution because the probiotic microorganisms frequently are highly sensitive to moisture. It is particularly advantageous to coat the coatings or layers from an alcoholic solution of the coating materials.

In another preferred embodiment, the oral administration form of the invention includes further nutritionally relevant additives in addition to the probiotic microorganisms. Preferably, it includes vitamins, minerals, trace elements, roughage, enzymes, vegetable extracts, proteins, carbohydrates, and/or fats. In case the oral administration form includes nutritionally relevant additives, such as proteins, which already begin to undergo digestion in the stomach, it is important that these nutritionally relevant additives are at least not entirely enclosed by an enteric coating.

Depending on the nutritionally relevant additives used, it may be necessary to incorporate each of these and/or each of these and the probiotic microorganisms in the oral administration form of the invention in a way so as to avoid contact with each other. In a preferred fashion, this is accomplished by incorporating the nutritionally relevant additives and/or microorganisms in different layers of a multilayer tablet.

Preferred vitamins are vitamin A (β-carotene), vitamin C, vitamin E, B complex vitamins, and/or vitamin K. Particularly preferred vitamins are vitamin A, vitamin C and/or vitamin E. As a rule, the amounts of these vitamins depend on the recommended minimum required dose for the respective vitamin, but these amounts may also be exceeded by 50 - 200% on an average. A preferred range for vitamin C is between 50

and 300 mg, for vitamin E from 10 to 50 mg, for vitamin A ≤1.5 mg, and for the B complex vitamins from 10 µg to 20 mg.

Preferred minerals are edible inorganic or organic salts of sodium, potassium, calcium, magnesium, zinc, and/or iron, preferably present as carbonates, bicarbonates, phosphates, biphosphates, sulfates, bisulfates, chlorides, fluorides, citrates, and/or lactates. The amount of minerals relative to the total weight of the oral administration form preferably is from 20 to 40 wt.-%. The oral administration form of the invention preferably includes silicon, chromium, manganese, iodine, molybdenum, selenium, and/or copper as trace elements.

The oral administration form of the invention preferably includes soy bran, corn bran, wheat bran, and/or grain shot as roughage, with soy bran being particularly preferred. The amount of roughage relative to the total weight of the oral administration form preferably is from 2 to 50 wt.-%.

Preferred enzymes and coenzymes are lipases and/or proteases, and coenzyme Q, superoxide dismutase and/or glutathione peroxidase which promote the function of stomach and/or intestine and/or the metabolism. They may be incorporated in *per se* known amounts and in a *per se* known form.

In addition, the oral administration form includes further probiotic substances, preferably oligofructose and/or other oligosugars.

Preferably, the vegetable extracts are dry extracts from *Echinaceae*, bioflavonoids, polyphenols, phytoestrogens, and/or saponins.

Preferably, the oral administration form of the invention includes soy protein and/or whey protein as proteins,

and/or as fats those fats which contain polyunsaturated fatty acids.

Depending on the respective embodiment, the oral administration form of the invention may also include conventional adjuvants and additives. The selection of adjuvants and/or additives also depends on the food-related regulations in that country where the oral administration form of the invention is to be used. Particularly in its coating, the oral administration form of the invention preferably includes plasticizers such as glycerol, Miglyol, mold wax, and/or acetylated monoglycerides as additional adjuvants.

Starch (e.g., corn starch), talc, microcrystalline cellulose, lactose, highly dispersed silica, polyvinylpyrrolidone, and/or cellulose powder are used as additional adjuvants and/or additives e.g. in the tablets, multilayer tablets, coated tablets of the invention. As further components, carbohydrates such as mannitol, sorbitol, xylitol, glucose, sucrose, fructose, maltose, dextrose, maltodextrin, and/or kaolin, and/or cellulose derivatives such as methylcellulose, hydroxypropylcellulose and/or hydroxypropylmethylcellulose, and/or calcium carbonate, calcium, magnesium and/or glycerol stearate can be used as binders and/or antitack agents. In addition, the oral administration form of the invention may also include colorants, flavors and/or aromatic substances, as well as lubricants, antioxidants and/or stabilizers. On the one hand, the amount of these basic substances depends on the desired content of probiotic microorganisms, vitamins, enzymes, roughage, etc. and, on the other hand, on criteria determining the mechanical-physical properties of the oral administration form, such as hardness, compactibility, size, color, and/or shape.

The oral administration form of the invention can be produced according to methods well-known to those skilled in the art. For example, these methods are known from H. Sucker,

P. Fuchs, P. Speisser, "Pharmazeutische Technologie", Stuttgart, 1978; or K.H. Farmer, K.H. Frömming, C. Führer, "Pharmazeutische Technologie", Stuttgart, 1986. They are hereby incorporated by reference and thus, represent part of the disclosure.

The invention is also directed to methods of producing an oral administration form of the invention, characterized in that the coating(s) is/are coated from an aqueous solution and/or from an organic solution, preferably from an organic solution, and more preferably from an alcoholic solution.

The coatings can be coated using conventional methods well-known to those skilled in the art, e.g. tablet coating, spraying of solutions, dispersions or suspensions, or by powder coating procedures.

The oral administration form of the invention is advantageous in that a substantially smaller amount of probiotic microorganisms is required to achieve the desired healthful effect. As a result, it can be produced much more cheaply.

Examples

The following examples are intended to illustrate the invention without limiting the general idea thereof.

Example 1

A mixture of 65% bacteria preparation, 6% microcrystalline cellulose, 20% tricalcium phosphate, 2% glyceryl palmitostearate, 0.6% magnesium stearate, and 6.4% disintegrant was compacted together with a mixture of vitamins and

minerals on an eccentric press E1 by Fette Company or KS by Kilian Company to form an oblong tablet having a core weight of 1.35 g and the dimensions 20.0 mm × 8.8 mm × 7.0 mm. To produce the enteric coating, shellac was initially dissolved in ethanol with stirring and as soon as a clear solution was obtained, Miglyol was added to the solution and stirring was continued for another 15 minutes. This solution was subsequently coated onto the tablet, using a Schlick nozzle. The process parameters were selected in a way so as to obtain homogeneous film coating. The amount of shellac was 2.1 wt.-% relative to the weight of the core, corresponding to 4.5 mg per cm^2 tablet surface.

Example 2

A mixture of 10% bacteria preparation, 33% lactose, 48.4% microcrystalline cellulose, 2% glyceryl palmitostearate, 0.6% magnesium stearate, and 6.0% disintegrant was compacted together with a mixture of vitamins and minerals on a rotary pelleter by Manesty Company to form an egg-shaped tablet having a core weight of 1.0 g and the dimensions 18.0 mm × 8.8 mm × 7.2 mm. Thereafter, a film of hydroxypropylmethylcellulose was coated thereon by spraying an ethanolic solution. The amount of coated hydroxypropylmethylcellulose was 0.8 wt.-% relative to the weight of the core, corresponding to 1.4 mg per cm^2 tablet surface. Then, also by spraying an ethanolic solution, another enteric coating comprised of shellac, polyvinylpyrrolidone and acetylated monoglycerides was coated over this first layer of hydroxypropylmethylcellulose. The amount of shellac was between 0.25 and 0.35 wt.-% relative to the weight of the core, corresponding to 4.5 mg/cm^2 - 6.3 mg/cm^2 tablet surface. The amount of acetylated monoglycerides and polyvinylpyrrolidone was 14.2 wt.-% each, relative to the amount of shellac employed.

Example 3

A mixture of 65% bacteria preparation, 6% microcrystalline cellulose, 20% tricalcium phosphate, 2% glyceryl palmitostearate, 0.6% magnesium stearate, and 6.4% disintegrant was compacted together with a mixture of vitamins and minerals on a rotary pelleter by Hata Company to form an egg-shaped tablet having a core weight of 1.35 g and the dimensions 21.0 mm × 10.0 mm × 8.0 mm. Thereafter, a film of hydroxypropylmethylcellulose and glycerol or Miglyol was coated thereon by spraying an ethanolic solution. The amount of coated hydroxypropylmethylcellulose was 0.8 wt.-% relative to the weight of the core, corresponding to 1.48 mg per cm^2 tablet surface. The amount of glycerol or Miglyol was 10 wt.-% relative to the amount of hydroxypropylmethylcellulose employed. Likewise by spraying an ethanolic solution, another enteric coating comprised of shellac, polyvinylpyrrolidone and acetylated monoglycerides was coated over this first layer of hydroxypropylmethylcellulose. The amount of coated shellac was between 0.3 and 0.5 wt.-% relative to the weight of the core, corresponding to 4.1 mg/cm^2 - 6.8 mg/cm^2 tablet surface. The amount of acetylated monoglycerides and polyvinylpyrrolidone was 14.2 wt.-% each, relative to the amount of shellac employed.